Remarks

Support for Claim Amendments and New Claims

Claim 71 has been amended to recite a solution at a concentration of more than 0.2 mg/ml of the recited protein. Support for this amendment is found on page 9, lines 22-23. Claim 73 has been amended, and claims 263-269 have been added, to recite other TFPI concentrations. See the paragraph bridging pages 9-10 as well as originally filed claims 2-4.

Claim 111 has been amended to recite a group of stabilizers and the stability of the claimed composition. Table 2 (right column) and Figure 9B set forth compositions comprising the recited stabilizers and having the recited half-life. Table 2, 7th entry, provides the half-life of the recited composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6.

New claims 270-274 recite TFPI, ala-human TFPI, or a mutein thereof in a solution having a solubilizer selected from the group consisting of phosphate, sulfate, and acetate at various concentration ranges (claim 270) or concentration levels (dependent claims 271-274). These claims are supported by Table 1 (see pages 28-31) and originally filed claims 48, 51, and 57.

New claim 275 recites TFPI, ala-human TFPI, or a mutein thereof in a solution having a solubilizer comprising phosphate at a concentration of greater than 20 mM or acetate, wherein the solution does not comprise urea. Support for the use of phosphate as a solubilizer at a concentration of greater than 20 mM is found on page 10, lines 4-5 of the specification. Support for the use of acetate is found in Table 1. Support for a solution comprising TFPI and a solubilizer in the absence of urea is found in Examples 6 and 11. Example 6 describes the

elution of TFPI into a buffer "without urea" (page 35, lines 7-8). Example 11 describes the solubilization, refolding, and purification of TFPI "in the absence of urea" (page 42, lines 14-15).

New claim 276 recites TFPI, ala-human TFPI, or a mutein thereof in a solution having a first solubilizer and a second solubilizer. Support for the recited solubilizers is found in Table 1 (pages 28-31).

New claims 277 and 278 recite an aqueous composition comprising TFPI, ala-human TFPI, or a mutein thereof and one of a group of recited stabilizers as well as a half-life of the recited polypeptide. Support for compositions having the recited stabilizers and recited half-life is found in Table 2, entries 1, 2, 3, 4, 6, 8, and 9 (see page 34) and in Figure 9B.

The amendments add no new matter.

Objections to the Specification

The Office Action requested that "NaPO4" be corrected to "Na_3PO_4." Applicants have made corrections to Table 1 and page 33, line 2.

The Office Action requested that "Tween" and "polysorbate" be identified as trademarks. The specification is amended to replace "Tween" with "TWEEN®" in Table 1. The term "polysorbate-80" is not a trademark; it is the name of the derivative of sorbitol and its anhydrides, copolymerized with about 80 moles of ethylene oxide. See Attachment 1.

The Office Action asserts that the specification does not provide antecedent basis under 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o) for the term "ala-human TFPI," which is recited in claims 71, 74, 77, 78, 108, 111, 128. Applicants respectfully traverse the objection. The specification teaches the isolation of human TFPI from human plasma. See page 4, line 30 to page 5, line 3 of the specification. The specification also teaches that TFPI can have an alanine

residue at its amino-terminal end. See page 19, lines 12-15 of the specification. "Ala-human TFPI," therefore, is human TFPI which has an alanine residue at its amino terminus. To advance prosecution, Applicants have amended claims 71, 74, 77, 78, 108, 111, and 128 to recite "human TFPI having the amino acid sequence shown in Figure 4 and having one further amino acid which is an amino-terminal alanine."

Applicants respectfully request withdrawal of these objections.

Objections to the Claims

As the Office Action suggests, Applicants amended claims 79, 80, 86, and 94-98, as well as claim 76, to recite "concentration from."

Applicants respectfully request withdrawal of these objections.

Information Disclosure Statement

Copies of some references cited in the Information Disclosure Statement filed November 30, 2001 were apparently not found in the file of parent application Serial No. 09/443,099. A Supplemental Information Disclosure Statement, together with copies of the missing references, accompanies this paper.

The Rejection of Claims 71-128 under 35 U.S.C. § 112, ¶ 2

Claims 71-128 are rejected under 35 U.S.C. § 112 ¶ 2. First, the Office Action contends that the term "TFPI," as recited in claims 71, 74, 77, 78, 108, 111, and 128, is indefinite. Applicants have amended these claims to spell out "Tissue Factor Pathway Inhibitor" followed by the parenthetical "(TFPI)." Second, the Office Action contends that the phrase "concentration of at least about," as recited in claims 115 and 118, is indefinite. Applicants have amended claims 115 and 118 to delete the recitation "about."

Applicants respectfully request withdrawal of these rejections.

The Rejection of Claims 71, 73, 78-80, and 110 and 114 Under 35 U.S.C. § 102(b)

Claims 71, 73, 78-80, and 110 and 114 are rejected under 35 U.S.C. § 102(b) as being anticipated by Broze, WO93/25230 ("Broze"). Applicants respectfully traverse this rejection.

To anticipate a claim, a prior art reference must disclose every element of the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 58 U.S.P.Q.2d 1286, 1291 (Fed.Cir. 2001). Independent claim 71 and dependent claim 73 recite a solution comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and "from 200 mM arginine to 300 mM arginine." Broze does not disclose a solution comprising "from 200 mM arginine to 300 mM arginine." Thus, Broze does not anticipate independent claim 71 or dependent claim 73.

Claim 78 and dependent claims 79, 80, and 110 recite a solution comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited solubilizers. Claim 78 has been amended to delete the solubilizers "sodium phosphate" and "sodium sulfate." Broze does not disclose any of the other recited solubilizers and therefore does not anticipate claims 78-80 or 110.

Independent claim 111 as amended and dependent claim 114 recite an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited stabilizers, as well as a level of stability (*i.e.*, a half-life at 40°C of the recited polypeptide, as determined using prothrombin time, which is greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6). Broze does not disclose any level of stability and therefore does not anticipate claims 111 and 114.

Applicants respectfully request withdrawal of this rejection.

The Rejections Under 35 U.S.C. § 103(a)

The Office Action makes the following rejections under 35 U.S.C. § 103(a):

- claims 73, 85, and 118 over Broze;
- claims 71 and 92 over Broze in view of Patel, U.S. Patent No. 5,358,708 ("Patel"); and
- claims 71, 73, 78, 81-83, 86, 87, 89, and 95-98 over Broze in view of Woog *et al.*, U.S. Patent No. 5,503,827 ("Woog").

Applicants respectfully traverse these rejections.

A *prima facie* case of obviousness requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. These requirements of a *prima facie* case of obviousness are not met for any of the three rejections under 35 U.S.C. § 103(a).

The primary reference, Broze

Broze is the primary reference in all of these rejections. Broze discloses the use of TFPI for the prophylaxis and treatment of sepsis and sepsis-associated coagulation disorders. Example 2 of Broze discloses a solution comprising 3.5 mg/ml TFPI in 150 mM sodium chloride and 20 mM sodium sulfate. Broze at page 20, lines 25-26. This TFPI composition was effective in preventing a drop in fibrinogen levels in baboons challenged with *E. coli*. Page 25, first paragraph. TFPI-treated baboons also had reduced organ pathology relative to control baboons. Page 25, lines 19-25.

Broze teaches that TFPI can be administered in "acceptable vehicles and solvents," including "water, Ringer's solution, and isotonic sodium chloride solution." Page 29, lines 30-32. Broze teaches that "[a] preferred injectable solution is LACI [*i.e.* TFPI] in an aqueous solution of 150 mM sodium chloride and 20 mM sodium phosphate." Paragraph bridging pages 29 and 30.

Broze is absolutely silent regarding TFPI solubility and stability. Broze does not hint at any solubility or stability problem with TFPI and offers no suggestion of how to improve these properties of TPFI in solution. In fact, based on Broze's stated success in treating sepsis with TFPI, it would not have occurred to one of ordinary skill to improve upon the solubility or stability of Broze's TFPI compositions.

The rejection of claims 73, 85, and 118 over Broze

Claim 73 recites a solution comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and "from 200 mM arginine to 300 mM arginine." Broze does not teach or suggest a TFPI solution comprising "from 200 mM arginine to 300 mM arginine." As discussed above, Broze is silent regarding TFPI solubility and therefore offers no teaching, suggestion, or motivation for improving TFPI solubility.

Claim 85 recites a solution having a pH from 5 to below 7.0 and comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited solubilizers. Independent claim 78 (and therefore dependent claim 85) has been amended to delete the solubilizers "sodium phosphate" and "sodium sulfate." Broze does not teach or suggest using any of the solubilizers recited in claim 85.

Claim 118 recites an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI polypeptide and having sodium chloride at a concentration of at least 500 mM, a pH from 5 to 10, and a half-life at 40°C of the polypeptide, as determined using prothrombin time, from 20 to about 70 days. Broze does not teach or suggest an aqueous composition with these characteristics. Absent Applicants' own teachings, one would not know which stabilizers at which concentrations and under what conditions would be effective to obtain the recited stability.

In summary, Broze does not teach or suggest at least one limitation of each of claims 73, 85, and 118: (i) a solution comprising 200 mM to 300 mM arginine as recited in claim 73, (ii) a solution comprising any of the solubilizers as recited in amended claim 85, or (iii) an aqueous composition having pH 5-10, at least 500 mM sodium chloride concentration, and level of polypeptide stability as recited in amended claim 118. Furthermore, Broze contains no

suggestion to modify its teachings to arrive at the compositions and solutions of claims 73, 85, or 118. The teachings of daily dosage levels, amounts of active ingredient in a single dose, dosage regimens, preparation forms, and combination therapies at page 29, line 1 to page 30, line 16, of Broze (which the Office Action cites) do not provide this suggestion or otherwise cure the deficiencies of Broze. Thus, Broze does not render claims 73, 85, or 118 *prima facie* obvious.

The rejection of claims 71 and 92 over Broze in view of Patel

The Office Action combines Patel with Broze to reject claims 71 and 92. Applicants respectfully traverse this rejection.

Independent claim 71 and claim 92 both recite a solution having a pH from 5 to 10 and comprising, *inter alia*, more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI. The solution of claim 71 comprises 200 mM to 300 mM arginine. The solution of claim 92 comprises the solubilizer histidine at a concentration from 5 mM to 20 mM. Broze does not disclose the use of arginine or histidine at any concentration. As discussed above, Broze is silent with respect to TFPI solubility or the need to improve stability using a solubilizer.

The Office Action cites Patel as teaching the use of histidine as a stabilizer for aqueous solutions of proteins including interferon, GM-CSF, or interleukin. The Office Action contends that "Patel's histidine is generically applicable to all proteins." See page 6 of the Office Action.

Patel teaches that histidine affects the stability of different proteins in different ways. Patel explains that, while histidine stabilizes glutamate synthetase, it has the opposite effect in creatine kinase. Col. 1, lines 12-23. "Thus, the art has recognized that different proteins exhibit widely varying inactivation responses." Col. 1, lines 23-27. Thus, Patel itself teaches that the use of histidine as a stabilizer is not generically applicable to all proteins.

Because the effect of amino acid stabilizers on any given protein is highly unpredictable, as taught in Patel, one of ordinary skill would not reasonably have expected that either arginine or histidine would stabilize TFPI solutions. The teachings of Patel would not have motivated one of ordinary skill in the art to stabilize solutions comprising TFPI with either arginine or histidine. Furthermore, the motivation to add solubilizers and/or stabilizers is lacking because the primary reference, Broze, does not disclose any need to improve TFPI stability.

The teachings of Broze and Patel, even if *arguendo* combined, do not provide the legally-required elements of a *prima facie* case that claims 71 and 92 are obvious.

The rejection of claims 71, 73, 78, 81-83, 86, 87, 89, and 95-98 over Broze in view of Woog

The Office Action combines Woog with Broze to reject claims 71, 73, 78, 81-83, 86, 87, 89, and 95-98. Applicants respectfully traverse this rejection.

Independent claim 71 (and its dependent claim 73) and independent claim 78 (and its dependent claims 81-83, 86, 87, 89, and 95-98) recite a solution having a pH from 5 to 10 and comprising more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI. The solution of claim 71 also comprises 200 mM to 300 mM arginine. The solution of claim 78 comprises one of a number of recited solubilizers. As discussed above, Broze is silent regarding TFPI solubility. Broze does not teach or suggest the use of arginine as recited in claim 71. Broze does not teach or suggest the use of any of the solubilizers recited in claim 78.

The Office Action cites Woog as teaching that sucrose, polyethylene glycol and glycine are "conventional stabilizers and solubilizers" and that sodium phosphate and sodium citrate are "conventional buffers." Office Action at page 5, 2nd paragraph. These teachings, however, do not cure the deficiencies of Broze.

Woog generically mentions a vast number of potential preservatives and "auxiliary substances" which may be used in pharmaceutical preparations. These "auxiliary substances" include stabilizing agents, organic hydrophilic polymers, buffers, structure formers, complexing agents, and wetting agents, and solubilizing agents. Col. 2, line 36; col. 7, lines 22-23; col. 7, line 31; col. 7, line 51; col. 8, line 28; and col. 9, line 4. Woog mentions a number of possible amino acids that may be used as stabilizers, solubilizers, or buffer substances in pharmaceutical forms of human proteins. These amino acids include arginine, lysine, ornithine, glycine, leucine, isoleucine, threonine, glutamine, glutamic acid, aminoacetic acid, phenylalanine, "as well as further amino acids mentioned in the Patent Applications EP 0430200 and EP 0306824." See Woog, col. 9, lines 3-11.

But Woog does not teach that any particular amino acids are effective as solubilizers, as opposed to stabilizers and buffer substances. Woog does not teach or suggest any concentrations of amino acid solubilizers, much less those recited in independent claim 71. Woog does not teach of suggest that any of the anions, polymers, amino acids, and other substances recited in amended independent claim 78 are effective in solubilizing proteins. Finally, Woog does not teach or suggest any particular types of proteins (*e.g.*, hydrophobic proteins such as TFPI), out of a vast number of possible "human proteins," which might benefit from solubilization using any of the recited solubilizers.

As discussed above, the primary reference Broze does not teach or suggest any need to improve TFPI solubility and/or stability. Thus, one of ordinary skill in the art would not have been motivated to look to Woog for suggestions of how to modify the TFPI preparations of Broze. Even if, *arguendo*, the ordinary skilled artisan had consulted Woog, Woog offers no guidance as to which solubilizers, from a vast number of possibilities, might be effective for any

particular protein. Furthermore, Patel teaches that the effect of amino acid stabilizers on any given protein is highly unpredictable. For these reasons, one of ordinary skill would have had no reasonable expectation of success in combining any of the large number of "auxiliary substances" disclosed in Woog with TFPI solutions.

The teachings of Broze and Woog, even if *arguendo* combined, do not provide the legally-required elements of a *prima facie* case that claims 71, 73, 78, 81-83, 86, 87, 89, and 95-98 are obvious.

New Claims 263-277

The arguments set forth above apply with equal force to new claims 262-277. Broze, Woog, and Patel, taken either alone or in combination, provide no teaching, suggestion, or motivation to use the solubilizers, solubilizer concentrations, or combinations of first and second stabilizers, or how to achieve the stability levels recited in these claims. Thus, claims 262-277 are patentable over any combination of Broze, Woog, and Patel.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

The Nonstatutory Double Patenting Rejection of Claims 71, 73, 78, 79, 109, and 110

Claims 71, 73, 78, 79, 109, and 110 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 9, 33-35, 37, and 41 of U.S. Patent No. 6,323,326. Applicants will consider submitting a Terminal Disclaimer when the pending claims are otherwise allowable.

Please continue to direct all correspondence in this application to T. Helen Payne, Esq., Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

BANNER & WITCOFF, LTD.

By: 

Lisa M. Hemmendinger
Registration No. 42,653

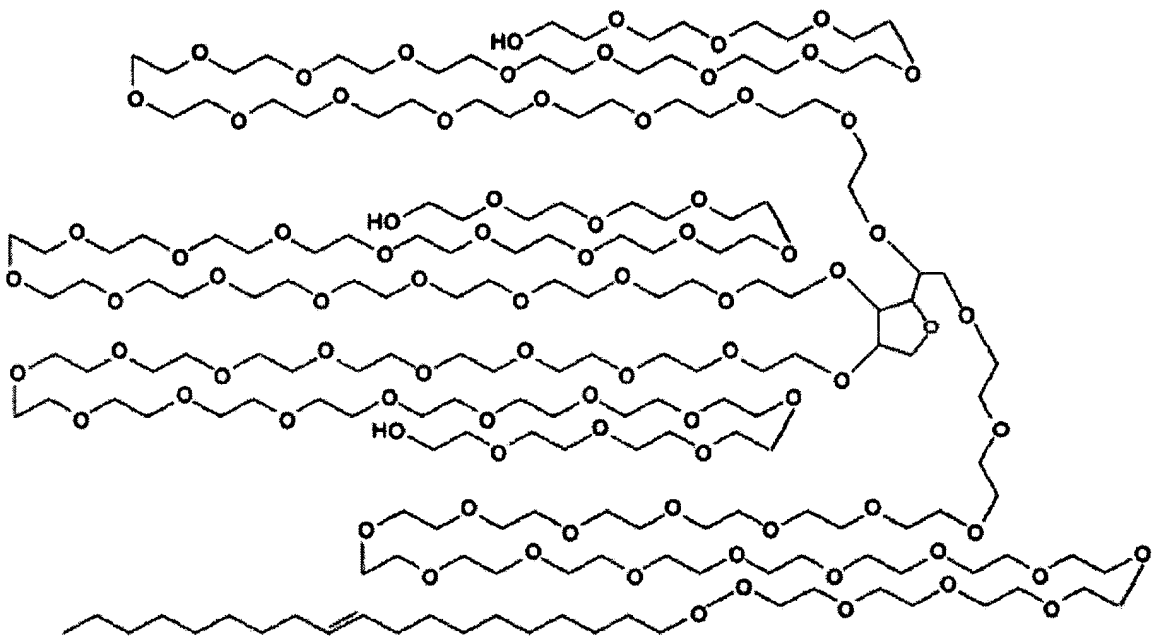
Date: November 16, 2004

Customer No. 22907

Ingredients --

Polysorbate 80

Chemical Formula:



polyoxyethylene sorbitan monooleate,
(x)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl)

Description
Amber colored viscous liquid

Uses

Polysorbate 80 is an emulsifying agent, often used in ice cream to prevent milk proteins from completely coating the fat droplets. This allows them to join together in chains and nets, to hold air in the mixture, and provide a firmer texture, holding its shape as the ice cream melts.

Similar compounds are polysorbate 60, polysorbate 65, etc.